Response to Office Action Mailed June 10, 2008

A. Claims In The Case

Claims 17-20, 22-30, 39, 41-80 have been rejected. Claims 48 and 56-59 have been amended. Claims 17-20, 22-30, 39, 41-47, and 49-80 have been canceled. Claims 81-97 have been added. Claims 48 and 81-97 are pending in the case.

B. Claim Objections

The pending claims were objected to for various reasons listed in the Office Action mailed June 10, 2008. Applicant has amended and/or deleted the objected to claims for clarification and believe that all of the Examiner's objections have been addressed.

C. New Claims

Support for new claims 81-97 may be found at least at paragraph [0051] and [0059] of Applicant's specification.

D. The Claims Are Not Indefinite Pursuant To 35 U.S.C. § 112, First Paragraph

Claims 22-24, 28-30 and 39 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully disagrees with the Examiner's rejections; however, to expedite prosecution claims 22-24, 28-30, and 39 have been canceled.

E. The Claims Are Not Anticipated By The Cited Art Pursuant To 35 U.S.C. § 102

The Office Action rejected claims 22, 23, 28, 29, 39, 49, 50, 53, and 80 as being anticipated by U.S. Patent No. 5,854,216 to Gaudreau ("Gaudreau"). Applicant respectfully disagrees with these rejections; however, to expedite prosecution these claims have been canceled.

The Office Action rejected claims 22, 25, 28, 39, and 80 as being anticipated by Coy et al. (*J. Med. Chem.*, **1985**, *28*, 181-5). Applicant respectfully disagrees with these rejections; however, to expedite prosecution these claims have been canceled.

The Office Action rejected claims 22, 25, 28, 39, and 80 as being anticipated by Lefrancois et al. (*Neuroendocrinology*, **1994**, *59*, 363-370). Applicant respectfully disagrees with these rejections; however, to expedite prosecution these claims have been canceled.

The Office Action rejected claims 22, 25, 28, 39, 41, 44, 47, and 80 as being anticipated by Campbell et al. (*J. Pept. Res.,*, **1997**, *49*, 527-537). Applicant respectfully disagrees with these rejections; however, to expedite prosecution these claims have been canceled.

F. The Claims Are Not Obvious Over The Cited Art Pursuant To 35 U.S.C. § 103(a)

The Examiner has rejected claims 17-20, 22-30, 39, and 41-80 as being unpatentable over Gaudreau.

In order to reject a claim as obvious, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Warner et al.,* 379 F.2d 1011, 154 USPQ 173, 177-178 (CCPA 1967). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must

be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), MPEP § 2143.03.

Claim 48 states:

A pharmaceutical composition, comprising:

a) a growth hormone-releasing hormone (GHRH) analogue or a pharmaceutically acceptable salt thereof in an amount effective to stimulate secretion or synthesis of growth hormone in a mammal in need thereof, said GHRH analogue or salt consisting of the formula: Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2; and

b) a pharmaceutically acceptable carrier.

The Office Action concedes that Gaudreau does not teach a pharmaceutical composition comprising the claimed GHRH analogues in the absence of conjugation to Ra-X. The Office Action, however, alleges that:

> "it would be obvious to make GHRH analogues consisting of the aforementioned peptides in the absence of conjugation to Ra-X and to dissolve them in a pharmaceutically-acceptable carrier such as water. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that the peptides possess biological activity, a binding affinity to the receptor in rat adenopituitary cells equivalent to or greater than that of wild type hGRF(1-29)NH_2 (Table 11).

The obviousness rejections appear to rely, at least in part, on the assertion that the teaching of a binding affinity to the receptor in rat adenopituitary cells would provide a basis for the determination of the analogue [D-Ala^{2}, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 as a likely candidate for use in a pharmaceutical composition. Applicant respectfully disagrees.

The presently claimed species (namely, "compound 8" in Gaudreau) is referred to in the present application as "compound 5," (see, e.g., Table 1, # 5 of the present application). Table 11 of Gaudreau discloses various *in vitro* properties of GHRH analogues 1-14. Specifically, Table 11 discloses the IC_{50} values and the relative affinities of each of the GHRH analogues for binding sites present on rat anterior pituitary cells (i.e., the relative affinity of a human GHRH analogue for the corresponding rat GHRH cell surface receptor). These are the only "biological" data that describe any properties of the specific GHRH species at issue.

The MPEP teaches that the "superiority of a property shared with the prior art is evidence of nonobviousness." Specifically, the MPEP states:

> Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness." No set number of examples of superiority is required. In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria).
> (MPEP, 716.02 (II)

Applicant has found, unexpectedly, that the binding affinity of the claimed GHRH analogue to the receptor in rat adenopituitary cells is not indicative of the binding affinity for the human GHRH receptor. Applicant notes that the difference between the binding affinity in the rat adenopituitary cells and the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK)

cells transfected with hGHRH-R was discovered during the course of Applicant's subsequent investigation. Applicant's specification states:

> [0061] Initial selection of a candidate from the original 14 polysubstituted GHRH analogues described in the U.S. Pat. No. 5,854,216 was based upon *in vitro* data on receptor affinity in 2-month old male Sprague Dawley rat anterior pituitary preparations. The new invention is based on the affinity of selected GHRH analogues for the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK) cells transfected with hGHRH-R, and on resistance to proteolysis in rat serum, human plasma or human serum. More precisely, the preferred drug candidates were selected, as compared to hGHRH(1-29)-NH_2, for: i--their increased relative binding affinity to hGHRH(1-44)-NH_2 binding sites in rat anterior pituitary *in vitro* as well as to hGHRH-R in BHK-expressing cells *in vitro*; and ii--their relative resistance to proteolysis in vitro.
>
> [0062] As can be noted from Table 1 below, the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor. As will be noted, from this point forward, GHRH analogues as presented in Table 1 will be referred to as GHRH analogues # 1 to 5. (*Emphasis added*)

Applicants discovery that "the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor" lead to the selection of the claimed GHRH analogue over many other analogues which, based on the teachings of Gaudreau, would appear to be more obvious for further testing.

The Office Action alleges that the data cited in Gaudreau in Table 11 provides the basis for a skilled artisan to investigate "all of the peptides recited in Gaudreau." Given that there are at least 30 peptides taught by Gaudreau (see for example, claim 3 of Gaudreau), it would be reasonable to assume that some sort of criteria would be used to identify which of the peptides should undergo further testing. As has been previously noted, compound 8 is not even among those peptides that are further tested for their ability to activate adenylate cyclase activity in cultured cells (see Gaudreau, Table 12, Col. 27, and text corresponding thereto). Based on the

initial testing with rat adenopituitary cells Gaudreau appears to teach away from the use of compound 8. Specifically, compound 8 was not deemed promising enough to undergo further testing. Gaudreau does not even claim a therapeutic use for Ra-X-Rb compound comprising compound 8 in claims 3 or 4. The Examiner is reminded that "teaching away from art is a per se demonstration of lack of obviousness." In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988); In re Fine, 837, F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant has found that [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 binds to the human GHRH receptor with >900X affinity than it binds to the rat GHRH receptor. The superior binding of [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 to human GHRH receptor is not taught or even suggested by any of the cited references. Gaudreau, which teaches the binding of the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 analogue to the rat GHRH receptor, would lead one of ordinary skill in the art to believe that the claimed [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 analogue would not bind to human GHRH receptor any better than the wild type hGHRH(1-29)-NH_2. This unexpected result renders the claims unobvious in view of case law and the guidance provided by the above-cited section of the MPEP.

In light of the above, Applicant respectfully submits that claims 48, 56-59, and 81-85 are unobvious and patentable over the teachings of Gaudreau, and respectfully requests the withdrawal of the 35 USC §103 rejections.

G. Many Of The Dependent Claims Are Separately Patentable

The Examiner is also respectfully requested to separately consider each of the dependent claims for patentability. Many of the dependent claims in addition to those mentioned above are independently patentable.

For instance, claim 81 recites "wherein the pharmaceutically acceptable carrier is sterile water." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 82 recites "wherein the pharmaceutically acceptable carrier is a saline solution." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 83 recites "wherein the pharmaceutically acceptable carrier is a buffered solution." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 84 recites "further comprising one or more diluents." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 85 recites "further comprising one or more stabilizers." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 86 recites "further comprising one or more preservatives." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 87 recites "further comprising one or more wetting agents." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 88 recites "further comprising one or more emulsifying agents." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 89 recites "further comprising one or more pH buffering agents." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 90 recites "further comprising one or more viscosity enhancing agents." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 91 recites "wherein the pharmaceutical composition is in a form suitable for injection." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 92 recites "wherein the pharmaceutical composition is in a form suitable for topical administration." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited art.

Claim 93 recites "wherein the pharmaceutical composition is in a form suitable for inhalation." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited.

Claim 94 recites "wherein the pharmaceutical composition is in a form suitable for intranasal administration." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited.

Claim 95 recites "wherein the pharmaceutical composition is in a form suitable for oral administration." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited.

Claim 96 recites "wherein the pharmaceutical composition is in a form suitable for transdermal administration." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited.

Claim 97 recites "wherein the pharmaceutical composition is in a form suitable for transmucosal administration." Applicant submits that this feature, in combination with the features of the independent claims, does not appear to be taught or suggested by the cited.

H. Summary

Based on the above, Applicant submits that all claims are now in condition for allowance. Favorable reconsideration is respectfully requested.

Applicant respectfully requests a two-month extension of time to respond to the Office Action dated June 10, 2008. A fee authorization form is enclosed for the extension of time fee. If any further extension of time is required, Applicant hereby requests the appropriate extension of time. If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Meyertons, Hood, Kivlin, Kowert & Goetzel, P.C. Deposit Account Number 50-1505/6165-09602/EBM

Respectfully submitted,

/Mark R. DeLuca/

Mark R. DeLuca
Reg. No. 44,649

Patent Agent for Applicant

MEYERTONS, HOOD, KIVLIN, KOWERT & GOETZEL, P.C.
P.O. BOX 398
AUSTIN, TX 78767-0398
(512) 853-8800 (voice)
(512) 853-8801 (facsimile)

Date: November 10, 2008